의학박사 학위논문

Neurological Complication Rates of Epidural Injections: A Comparison of Steroid Use Patterns

경막외 주사의 신경학적 합병증의 발생률: 스테로이드 제제간 비교연구

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황 병 관

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지도교수 박 병 주

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Neurological Complication Rates of Epidural Injections: A Comparison of Steroid Use Patterns

By

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A Thesis submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Medicine (Preventive Medicine) at the Seoul National University College of Medicine

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Abstract

Neurological Complication Rates of Epidural Injections: A Comparison of Steroid Use Patterns

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Background: Epidural injections are popular pain management procedures, but steroid usage of epidural injections has been debatable due to its safety concerns.

Objective: We aimed to estimate the incidence rates of neurological complications after epidural injections by establishing retrospective cohort using insurance claim data and compare the incidence rates of neurological complication between steroid use patterns.

Methods: Using a national insurance claims database, we identified patients who received at least one epidural injection or selective nerve root block with spine-related ICD-10 codes from 2009-2013. We excluded patients who received one inpatient care or two outpatient cares under neurological complication-related ICD-10 codes, including stroke, spinal cord infarction, quadriplegia, paralysis, visual loss or even death in 2009. We estimated incidence rates and hazard ratios in propensity score-matched cohorts stratified by steroids, using the Charlson comorbidity index, age, gender, local anesthetics, and anti-thrombotics as variables. We included cases admitting to hospital within 24 hours after injections and treated for neurological complications-related ICD-10 codes.

Results: During the study period, triamcinolone was the most popular steroid (53.8%) but after a change of insurance approval (March 15, 2013), usage of dexamethasone and non-steroid injections was on the increase. We estimated neurological complication incidence rates after injections with steroids versus those without steroids were 1.48 per 100,000 person-days (95% CI 1.25–1.65) versus 0.86 per 100,000 person-

days (95% CI 0.66–1.30). Incidence rates of neurological complications due to injections with particulate steroids and non-particulate steroids were 1.73 per 100,000 person-days (95% CI 1.41–1.95) and 0.90 per 100,000 person-days (95% CI 0.43–1.47), respectively. The adjusted hazard ratio (aHR) of neurological complications due to steroid injections compared to non-steroid injections was 1.71 (95% CI 0.96–2.49). The aHR of neurological complications due to injections with a particulate steroid compared to those with a non-particulate steroid was 1.92 (95% CI 0.96–4.53). The aHR of particulate versus non-particulate steroid injections was 4.98 (95% CI 1.01-262.35), at the cervicothoracic level. Further, the aHR of neurological complications for non-particulate steroid compared to non-steroidal injections was 0.97 (95% CI 0.46-3.01).

Conclusion: The incidence rate of neurological complications with particulate steroid injections was higher than that after non-particulate steroid injections at the cervicothoracic level. In addition, injections with non-particulate steroids was as safe as epidural injections without steroids.

Key words: Epidural injection; Steroids; Neurological complications; Propensity score matching

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1. Introduction

1.1. Background

Low back pain is one of the most significant global public health problems [1], with an estimated lifetime prevalence of 58-84%. More than 20% of the patients with persistent low back pain are likely to have another episode within the next year [2, 3]. Neck pain is another common musculoskeletal condition, with a lifetime prevalence of 14.2-71% (mean: 48.5%) [4, 5]. The healthcare burden of low back and neck pain has increased substantially over the last several decades, along with growth in the aged population in the world [1]. Therefore, it is important to develop strategies to prevent, treat, and rehabilitate patients with these often debilitating conditions.

If patients present with low back and neck pain without red flag signs (i.e. loss of control of the bladder or bowel, significant weakness, fever, or saddle anesthesia), many practice guidelines recommend starting with non-surgical management, including behavioral modifications, physical therapy, and pharmacologic therapy [6]. However, if patients fail to see any benefit with more conservative treatment, physicians may consider interventional treatments. Among a plethora of therapeutic options for low back and neck pain, epidural injections are preferentially used to manage these types of pain [7]. These injections are less invasive than surgery and are effective in reducing pain, restoring function, reducing the need for additional healthcare, and avoiding surgery [8]. Such injections are now routinely image-guided, allowing for accurate introduction of medications into the affected spinal level and minimizing potential complications [9]. Consequently, the use of injections has increased dramatically in the last several decades [7].

The most common agents used during epidural injections are local anesthetics and glucocorticoid steroids. Local anesthetics interrupt neuronal signaling by blocking voltage-gated sodium channels, whereas corticosteroids presumably work by inhibiting the release of the inflammatory cytokines induced

by phospholipase A2 [10, 11]. Further, corticosteroids can directly inhibit nociceptive C-fiber neuronal membrane excitation [12].

Corticosteroids can be classified as particulate or non-particulate. Particulate steroids were popular for use in epidural injections previously because they tend to persist in the epidural space longer than non-particulate steroids and may thus elicit a more durable anti-inflammatory effect [13]. However, the use of particulate or nonparticulate steroids for this purpose is considered off-label by the Food and Drug Administration (FDA), which has not approved the use of any injectable steroids for epidural administration. Furthermore, the safety of these epidural injections has not been established [14]. Increasing the number of procedures raises concerns about the overall safety of these procedures because several case reports and Closed Claims Studies have demonstrated serious neurological complications and long-term disabilities in patients after steroid injections [15]. Furthermore, a multi-state outbreak of fungal infections in 2012 resulted in the deaths of more than 100 patients. This outbreak was due to contamination of compound steroids manufactured by one pharmacy and raised public concerns about the safety of epidural steroid injections more broadly [16].

In 2014, the U.S. Food and Drug Administration (FDA) issued a warning that injections of corticosteroids into the spinal epidural space may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death [17]. This warning is based on an analysis of 90 cases resulting in serious neurologic events, which was reported in the FDA Adverse Event Reporting System (FAERS) database and in the medical literature between 1997 and 2014. Accordingly, the Korean Ministry of Food and Drug Safety (KFDA) and Health Insurance Review & Assessment Service (HIRA) withdrew insurance approval for triamcinolone, one of particulate steroids, for epidural injections in March of 2013.

Despite this U.S. FDA's announcement fueled expert debates because it did not distinguish between risk related to injection approaches (transforaminal, interlaminar, or caudal), anatomical levels (cervical, thoracic, lumbar, or sacral), and steroid types (particulates or non-particulate) [18]. Therefore, some pain

experts have criticized this announcement as a form of overregulation because neurological complications are rare given the large number of procedures performed [17].

One proposed mechanism underlying some serious neurologic complications of epidural injections is embolization of the segmental or vertebral artery by particulate steroids [19]. An expert multidisciplinary working group published a consensus opinion on this risk, suggesting that cervical transforaminal injections of particulate steroids was a major potential risk factor for these catastrophic neurological complications [20]. However, this statement was based on microscopic laboratory studies, anatomical animal studies, case series, and survey data analyses, but not epidemiologic evidence. Therefore, population-based studies are needed to establish a valid estimate of the incidence of serious neurologic complications [14].

The HIRA database contains all claims made by public Korean hospitals and private practitioners; over 99% of these are collected electronically. The National Insurance System is a mandatory insurance system and includes 97% of all Koreans. The HIRA database has been used for epidemiological studies because of its minimal healthy user bias and strong representativeness and generalizability [21]. Serious neurological complication rates are also likely extremely low in this dataset because neurological complications are themselves rare and medicolegal problems further prevent physicians from reporting procedural complications. Given these limitations, it is difficult to establish a valid incidence estimate of neurological complications from prospective cohort studies, particularly when given time and cost limitations. Therefore, a larger analysis of HIRA database data will allow for more accurate estimation of the incidence of rare complications [22].

1.2. Purpose of this study

The primary purpose of the present study was to estimate the incidences of acute neurological complications after epidural injections. In addition, we aimed to determine the safest steroid using HIRA database data, and to investigate other potential risk factors, including procedure level, local anesthetics, age, and comorbid conditions that might increase the risk for serious neurological complications after epidural injections. We also evaluated whether the KFDA insurance withdrawal of triamcinolone decreased neurological complication rates. Our findings may have a significant impact on determining improved correct policy approaches and guiding future clinical decision-making.

2. Materials and methods

2.1. Data Source

Data from the HIRA database collected between 2009 and 2013 were obtained, after appropriate approvals were obtained from HIRA for the use of these data for academic research. All data were stored on a password-protected server, which was maintained by HIRA. To protect patient privacy, claims data were extracted using anonymized identifiers provided by HIRA in accordance with the Act on the Protection of Personal Information Maintained by Public Agencies [21]. The HIRA database contains data gathered from clinical care administered via the Korean National Health Insurance Scheme, the Medical Assistance Program, and the Medical Care for Patriots and Veterans Affairs Scheme. This database contains 1) administrative data (e.g., sex, age, hospital identifiers, and region); 2) clinical treatment data (e.g., procedural code, classification code, dose, frequency, days' supply, general name code, and direct medical costs); 3) diagnostic data [e.g., *International Classification of Disease, Tenth Revision*-10 (ICD-10) codes, diagnosis hierarchy codes, and medical specialty codes]; and 4) prescription data, including dose, frequency, supply duration (days), and general drug name code (Table 1) [22]. From this database, we were able to determine treatment types (i.e. medications, rehabilitation-physical therapy, procedures, or surgeries) and specific ICD-10 diagnoses at each clinical encounter.

Table 1. Contents of raw data from Korean National Health Insurance Review and Assessment Service and list of variables

Tables	List of variables	Identifiers
Administration (t20)	De-identified patient number, sex, age, hospital identifier, region, admission date	Claims identifier
Treatment (t30)	Procedural code, classification code, dose, frequency, days' supply, general name code, and direct medical costs	
Diagnosis (t40)	*International Classification of Disease, Tenth Revision* ICD-10, diagnosis hierarchy code, and medical specialty code	
Prescription (t53)	Dose, frequency, days' supply, general name code	

2.2. Ethical Considerations

The present study was approved by the Seoul National University Hospital Institutional Review Board, which waived the need for informed consent due to our use of a database containing anonymized identifiers (E-1307-038-501).

2.3. Retrospective Cohort Construction

The source population included adults (aged 20-100 years) who visited outpatient clinics between January 1, 2009 and December 31, 2013. All participants underwent at least one epidural injection or nerve root block and had spine-related ICD-10 code diagnoses (Table 2). We classified injections with ICD-10 codes as neck pain, thoracic pain, cervical radiculopathy, or thoracic radiculopathy as cervicothoracic epidural injections. For injections with ICD-10 codes indicating back pain, sacral pain, or lumbosacral radiculopathy, the term 'lumbosacral epidural injections' was used as a more global classifier. All epidural blocks and selective nerve root blocks were classified by their anatomical level, with the appropriate procedure codes [LA321 (cervicothoracic epidural block), LA322 (lumbosacral epidural block), LA353 (caudal block), or LA354 (selective nerve block)] (Table 3). We divided selective nerve root blocks into cervicothoracic or lumbosacral injections, depending on the anatomical location relevant to the ICD-10 code. For example, if the ICD-10 code indicated low back pain and the procedure code indicated a selective nerve root block, the case was classified as a lumbosacral injection.

Table 2. The ICD-10 codes used for identifying cervico-thoracic and lumbosacral pain.

ICD-10	Diagnosis of cervico-thoracic and lumbo-sacral pain
G54.2/G54.3/G54.4/G54.8/G54.9/G55/G89	Cervical root disorders, not elsewhere classified/Thoracic root disorders, not elsewhere classified/Lumbar root disorders, not elsewhere classified/Other nerve root and plexus disorders/Nerve root and plexus disorder, unspecified/Nerve root and plexus compressions in diseases classified elsewhere/ Acute and chronic pain, not elsewhere classified
M43/M46.1/M47/M48/M49	Other deforming dorsopathies/Sacroiliitis, not elsewhere classified/Spondylosis/Other spondylopathies/Spondylopathies in diseases classified elsewhere
M50/M51/M53/M54	Cervical disc disorders/Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders/other and unspecified dorsopathies, not elsewhere classified/Dorsalgia
M79.2/M79.6	Neuralgia and neuritis, unspecified/Limb pain
R52	Pain, unspecified

Table 3. Insurance claim codes of procedures. (the Health Insurance Record Review & Assessment Service in January 2011)

Codes of injections	Name of procedures
LA321	Epidural block (Cervicothoracic)
LA322	Epidural block (Lumbosacral)
LA353	Caudal block
LA354	Selective nerve root block

The study population included patients who received at least one injection after the index date (January 1, 2010). We excluded patients with a history of neurological complications (including strokes, transient ischemic attacks, retinal vascular occlusion, myelopathy, spinal cord injury, neurogenic bladder, hemiplegia, tetraplegia, or death) up to one year before the index date (Table 4). A history of neurological complications was determined if a subject was admitted to the hospital or had more than two outpatient clinic visits associate with neurological complication ICD-10 codes before the index date (Figure 1 and 2). We also excluded patients with a history of spinal surgery prior to the index date (Table 5).

We excluded inpatient procedures because there were no data available on the amount of time that elapsed between the day of the procedure and that on which complications first occurred. This was because all inpatient insurance claims were requested together each month. However, most (93.7%) procedures were outpatient. We further excluded injections without associated fluoroscopic or CT data because these were presumed to be blind injections. Finally, we excluded data for cases in which injections containing more than two different steroids were performed on the same day.

Table 4. The ICD-10 codes defining neurological complications.

ICD-10	Diagnosis of Neurological Complications
I60-69/G45/G46/H34.0/H34.1/H34.2/H34.9	Cerebrovascular diseases/Transient cerebral ischemic attacks and related syndromes/Vascular syndromes of brain in cerebrovascular diseases/Transient retinal artery occlusion/Central retinal artery occlusion/Other retinal artery occlusions/Unspecified retinal vascular occlusion
G95.1/G95.2/G95.9/G83.4/G95.8/N31/G81/G82/G83	Vascular myelopathy (Acute infarction of spinal cord)/Cord compression, unspecified/Disease of spinal cord, unspecified, Myelopathy NOS/Neurogenic bladder due to cauda equine syndrome/Other specified diseases of spinal cord, Cord bladder NOS/Neuromuscular dysfunction of bladder, not elsewhere classified/Hemiplegia/Paraplegia, Tetraplegia/Other paralytic syndromes
I46.8/I46.9/R96/R98/R99	Cardiac arrest due to other underlying condition/Cardiac arrest, cause unspecified/Other sudden death, cause unknown/Unattended death/Other ill-defined and unspecified causes of mortality

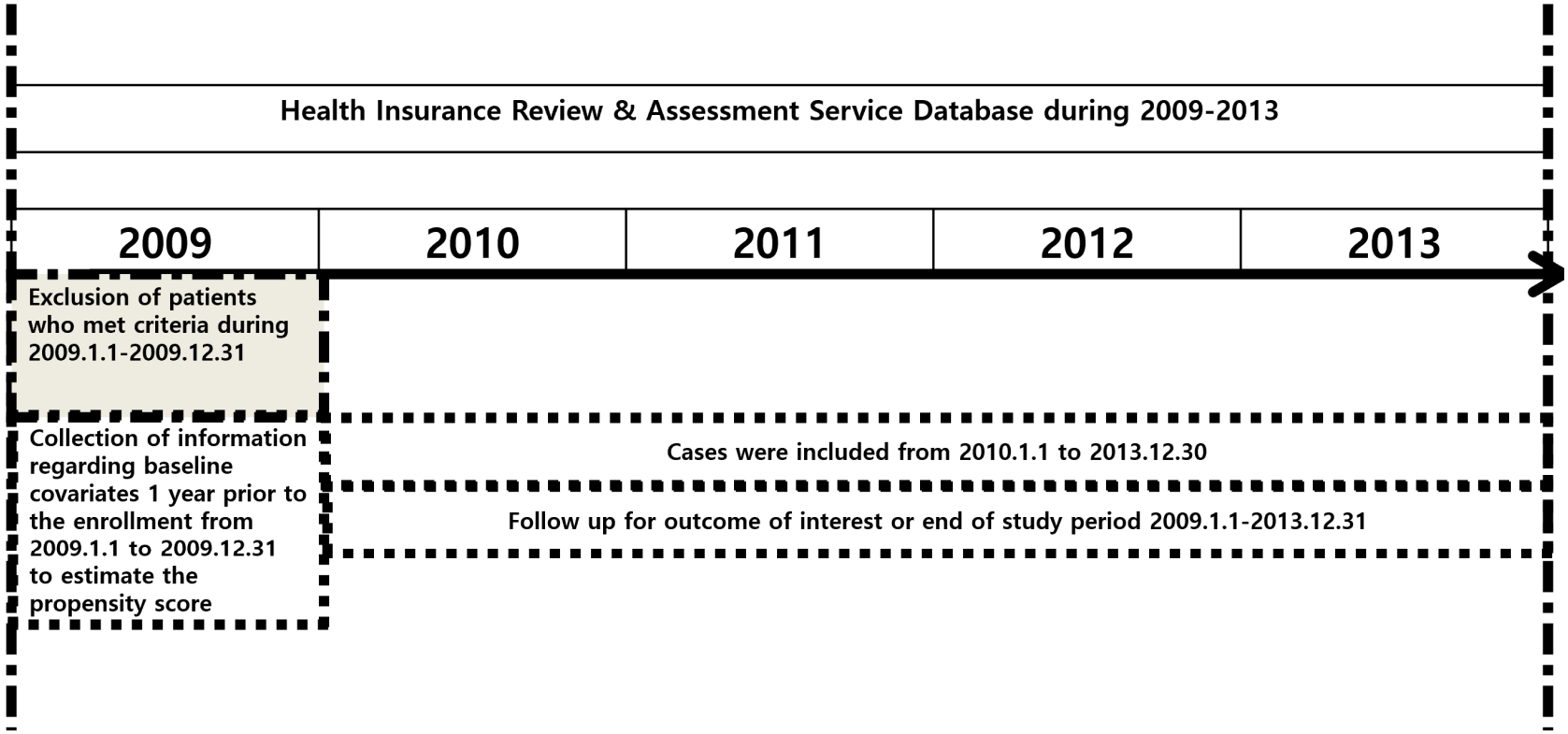

Figure 1. Schematic description of the study periods. The cohort comprised patients with more than one injection, without previous neurological diseases. Cases of acute neurological complications were admitted to hospital within 24 hours of injections at an outpatient clinic.

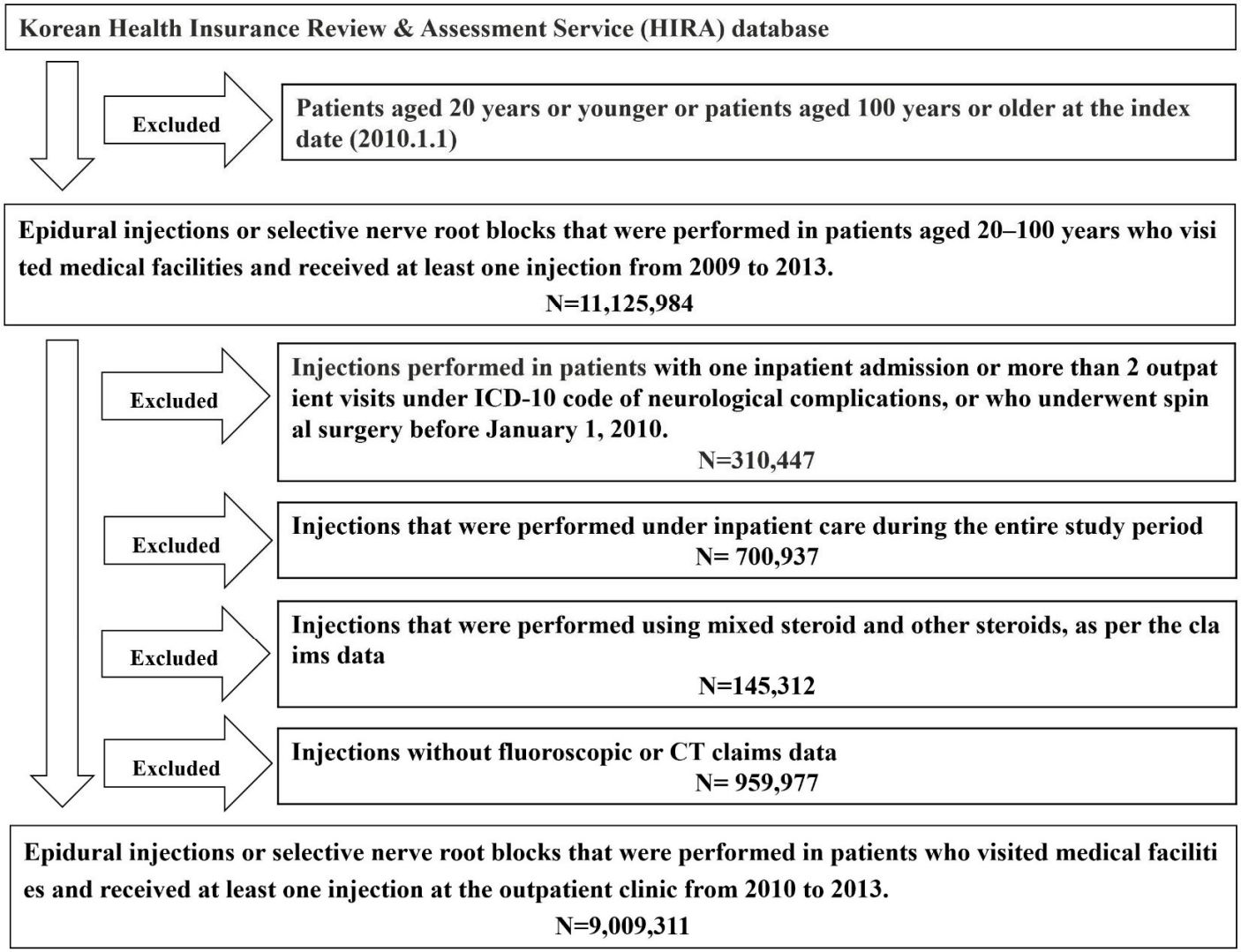

Figure 2. The flowchart of participants who received epidural injections or selective nerve root blocks.

Table 5. Insurance claim codes of spine surgeries used in the Health Insurance Record Review & Assessment Service.

Codes of spinal operations	Name of procedures
N0444, N0445, N0451, N0452, N0453	Arthrodesis for spinal deformity & vertebral corpectomy
N2461, N2462, N2463, N2464, N2465, N2466, N0466, N2467, N2468, N2469, N0468, N0469, N2470, N2471, N2472	Arthrodesis of spine
N1497, N1498, N1499, N2491, N2492, N0480, N0630	Laminectomy, laminoplasty & sacroplasty
N1491, N1492, N1493, N1494, N1495, N1496	Discectomy
N0471, N0472, N0473, N0474, N0480, N0630	Other spine operations (vertebroplasty, kyphoplasty. Operation of spina bifida, close reduction of fracture)

2.4. Working Definition for New Cases

We defined cases with neurological complications as patients 1) who received epidural injections or selective nerve root blocks at the outpatient clinic after the index date (January 1, 2010), 2) who were admitted to the hospital or visited the emergency room within 24 hours after receiving an injection, and 3) who were treated for an ICD-10 code for a neurological complication during their hospitalization or who died in the hospital. In Korea, outpatient and inpatient insurance claim data are separately submitted to the HIRA. Thus, if the patient was admitted to the hospital after receiving an injection at an outpatient center, two different claim sets were generated: one each from outpatient and inpatient visits. Given this, we were able to obtain accurate injection and admission dates (Figure 3).

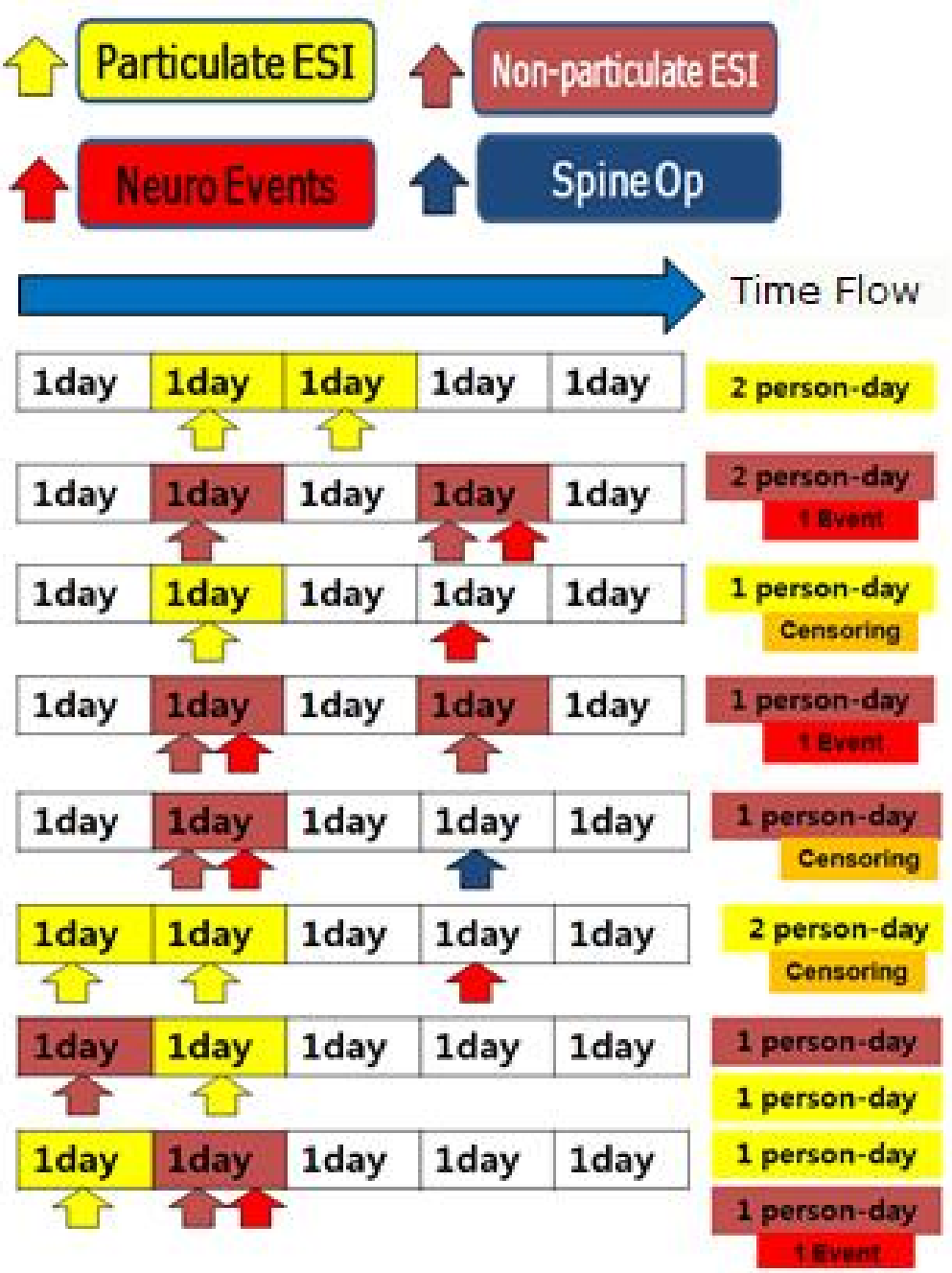

Figure 3. Flow chart to estimate neurological complications rates by epidural injections by steroid use patterns.

2.5. Collecting Covariates

We determined currently available injectable steroids, local anesthetics, and blood thinners from EzDrug and Kimsonline in South Korea (Table 6). Personal and procedure-related information such as age, gender, level of injection (cervicothoracic epidural injections, lumbosacral epidural injections, or caudal block), steroid type (triamcinolone acetonide, methyl-prednisolone sodium succinate, betamethasone sodium phosphate, or dexamethasone disodium phosphate), type of mixed local anesthetic (lidocaine, bupivacaine, mepivacaine, ropivacaine, or others), and blood thinner treatment (antiplatelet drugs and anticoagulants) was collected for each case.

In Korea, betamethasone acetate (a particulate steroid) was not manufactured and betamethasone sodium phosphate (non-particulate steroid) was the only commercially available injectable steroid solution [23]. Therefore, we categorized steroid into two groups: particulate steroids (triamcinolone acetonide and methyl-prednisolone sodium succinate) and non-particulate steroids (betamethasone sodium phosphate and dexamethasone disodium phosphate) [23]. We then calculated incidence rates of neurological complications per 100,000 person-days per injection.

Age, gender, local anesthetics, and treatment with blood thinners (antiplatelet drugs and anticoagulants) were considered possible confounding factors. We calculated modified Charlson index scores to estimate disease severity, according to previous diagnoses within one year prior to the index date, which was also a potential confounding factor (Table 7) [24].

Table 6. The dosage, ATC codes, and insurance codes of corticosteroid, local anesthetics, anticoagulants, and antiplatelet drugs.

Drug	Dosage	ATC code	Insurance codes
Triamcinolone acetonide	200 mg 40 mg 50 mg	H02AB08	243301BIJ 243303BIJ 243305BIJ
Methylprednisolone sodium succinate	200 mg 40 mg 125 mg 250 mg 40 mg 500 mg	H02AB04	193501BIJ 193502BIJ 193601BIJ 193602BIJ 193603BIJ 193604BIJ
Betamethasone sodium phosphate	9 mg/ml 4 mg/ml	H02AB01	316100BIJ 116502BIJ
Dexamethasone disodium phosphate	5 mg/ml 4.37 mg/ml 4 mg/ml	H02AB02	142201BIJ 142202BIJ 142203BIJ
Lidocaine	20-100mg with epinephrine	N01BB02, N01BB52	183903BIJ, 183904BIJ, 183905BIJ, 183906BIJ, 183907BIJ, 183908BIJ 314200BIJ, 314300BIJ, 314400BIJ, 314500BIJ
Mepivacaine	54mg, 400mg	N01BB03	190401BIJ, 190402BIJ
Bupivacaine	20-100mg with epinephrine	N01BB01, N01BB10, N01BB51	120101BIJ, 120104BIJ, 120106BIJ 430601BIJ, 430602BIJ, 430603BIJ
Ropivacaine	20mg-200mg	N01BB09	225001BIJ, 225002BIJ, 225003BIJ, 225004BIJ
Procaine	20mg	N01BA02	218202BIJ
Tetracaine	20mg	N01BA03	236501BIJ
Articaine	with epinephrine	N01BB58	450200BIJ, 513200BIJ

Aspirin	75 mg 81 mg 100 mg 500 mg	B01AC06	111002ATE 111003ACE, 111003ATE 110701ATB, 111001ACE, 111001ATE, 110801ATB 110702ATB, 110802ATB
Clopidogrel	75 mg	B01AC04	136901ATB, 492501ATB, 495201ATB, 501501ATB, 498801ATB
Aggrenox	200 mg+25 mg	B01AC30	269400ATB
Dipyridamole	25 mg 75 mg	B01AC07	147201ATB 147203ATB
Triflusal	300 mg 300 mg 150 mg	B01AC18	244101ACH 244101ACE 244102ACH
Cilostazol	50 mg 100mg	B01AC23	133202ATB 133201ATB, 133203ATR, 133201ACR
Prasugrel	5 mg 10 mg	B01AC22	597301ATB 597302ATB
Ticagrelor	60 mg 90 mg	B01AC24	615901ATB
Warfarin	2 mg 5mg	B01AA03	249103ATB 249105ATB
Heparin	20 ml 5 ml 1ml 100 ml 500 ml 1000 ml	B01AB01	168601BIJ 168602BIJ 168603BIJ 168605BIJ 168606BIJ 168607BIJ
Enoxaparin	10 mg 20 mg 40 mg 60 mg 80 mg	B01AB05	152101BIJ 152102BIJ 152103BIJ 152104BIJ 152105BIJ
Ribaroxaban	10 mg 15mg 20 mg	B01AF01	511401ATB 511402ATB 511403ATB

Apixaban	2.5 mg 5 mg	B01AF02	617001ATB 617002ATB
Dabigatran	110 mg 150 mg	B01AE07	613701ACH 613702ACH

Table 7. Diseases, ICD-10 codes, and their weights used to calculate the Charlson comorbidity index [22].

Disease	ICD-10 Code	Weight
Myocardial infarction	I21, 22, 252	1
Congestive heart failure	I43, 50, 110,130, 132, 255, 420, 425, 426, 427, 428, 429, P290	1
Peripheral vascular disease	I70, 71, 731, 738, 739, 771, 790, 792, K551, 558, 559, Z958, 959	1
Cerebrovascular disease	G45, 46, I60, 61, 62, 63, 64, 65, 66, 67, 68, 69, H340	1
Dementia	F00, 01, 02, 03, G30, F051, G311	1
Chronic pulmonary disease	J40-47, J60-67, I278-279, J684, J701, J703	1
Connective tissue disease	M05, 32, 33, 34, 06, 315, 351, 353, 360	1
Peptic ulcer disease	K25-28	1
Mild liver disease	B18 K73, K74, K700-703, K709, K713, K714, K715, K717, K760, K762-764, K768, K769, Z944	1
Diabetes without complications	E10, E11, E12, E13, E14, E100, E101, E106, E108-111, E116, E118-121, E126, E128-131, E136, E138-141, E146, E148-149	1
Diabetes with complications	E102-105, E107, E112-114, E115, E117, E122-125, E127, E132-137, E142-145, E147	2
Hemiplegia	G81, G82, G041, G114, G801, G802, G830-834, G839	2
Moderate to severe renal disease	N18, N19, N052-057, N250, I120, I131, N032-037, Z490-492, Z940, Z992	2
Any tumor including leukemia and lymphoma	C00-26, C30-34, C37-41, C43, C45-58, C60-76, C81-85, C88, C90-97	2
Moderate or severe liver disease	K704, K711, K721, K729, K765-767, I850, I859, I864, I982	3
Metastatic solid tumor	C77-80	6
AIDS/HIV	B20-22, B24	6

2.6. Propensity Score Matching

Using propensity score-matched cohort, we estimated incidence rates of neurological complications by steroid use patterns and hazard ratios. To estimate propensity scores, we collected information regarding baseline covariates before the index date, including age, gender, Charlson comorbidity index score, anatomical level of injection, local anesthetic, and blood thinner use. After then, we estimated propensity scores for adding steroids to injections, without regard for outcomes, by multiple logistic regression analyses, using collected variables [25, 26]. We assessed model calibration with Hosmer-Lemeshow good-of-fit test and model discrimination with the C-statistic. Matching (1:1) was carried out with the Greedy algorithm and the estimated propensity scores [25]. We compared baseline characteristics using standardized differences between comparison groups. Cohen's d was calculated as the difference between two sample means, divided by the standard deviation for all pooled data. We defined imbalance as an absolute value greater than 0.1. We performed three different propensity score estimations and matching of non-steroid injections versus steroid injections, non-particulate steroid injections versus particulate injections, and non-particulate injections versus non-steroid injections.

2.7. Sample Size Calculation

We calculated sample size using PASS 12.0 (NCSS PASS, Kayswille, Utah, USA) with statistical power [Type I error (α) = 0.05 and Type II error (β) = 0.8] using a Cox regression model including relative risks of neurological complications, incidence rates, and exposure ratios for non-particulate vs particulate steroid use (Table 8).

Table 8. Calculated Sample Size.

Model	RR*	Power	Exposure ratio	Sample Size
Cox regression	10.0	0.8	1:9	234,980
		0.8	2:8	132,177

***RR: Relative Risk**

2.8. Statistical Analyses

SAS Version 9.2 (SAS Institute, Cary, NC) was used for analyses. We summarized demographic characteristics as frequencies and percentages for categorical variables. We estimated the incidence rates of neurological complications per 100,000 person-days by dividing the number of neurological complications by the total number of person-days at risk and multiplying the result by 100,000. We calculated 95% confidential intervals (CIs) assuming a Poisson distribution and used the matched Cox regression model to estimate hazard ratios and 95% confidence intervals for neurological complications in the propensity score-matched cohorts. To compare between steroid and non-steroid injection cases, we set non-steroid injections as the reference and estimated adjusted hazard ratios (aHRs). We also set non-particulate steroid injections as a reference and estimated the aHRs for particulate steroid injections and non-steroid injections. Statistical significance was set at a *P* value of less than 0.05. Lastly, a sensitivity analysis was then performed to include a washout period of up to 2 years. In addition, we tried to compare the differences of incidence rates when we included all neurological complications up to day 3 or day 7 after epidural injections.

3. Results

3.1. The Change of Steroid Use Pattern after the Insurance Policy Change

A total of 11,125,984 epidural injections were performed during the study period (Figure 2). The total number of injections increased yearly (Figure 4). Before March 15, 2013 (the change of the insurance approval by the Ministry of Food and Drug Safety), triamcinolone was the most popular steroid for epidural injections. After March 15, 2013, the number of dexamethasone injection and injections without steroids increased. To estimate incidence rates of neurological complication, we included 9,009,311 injections in the analysis (Figure 2).

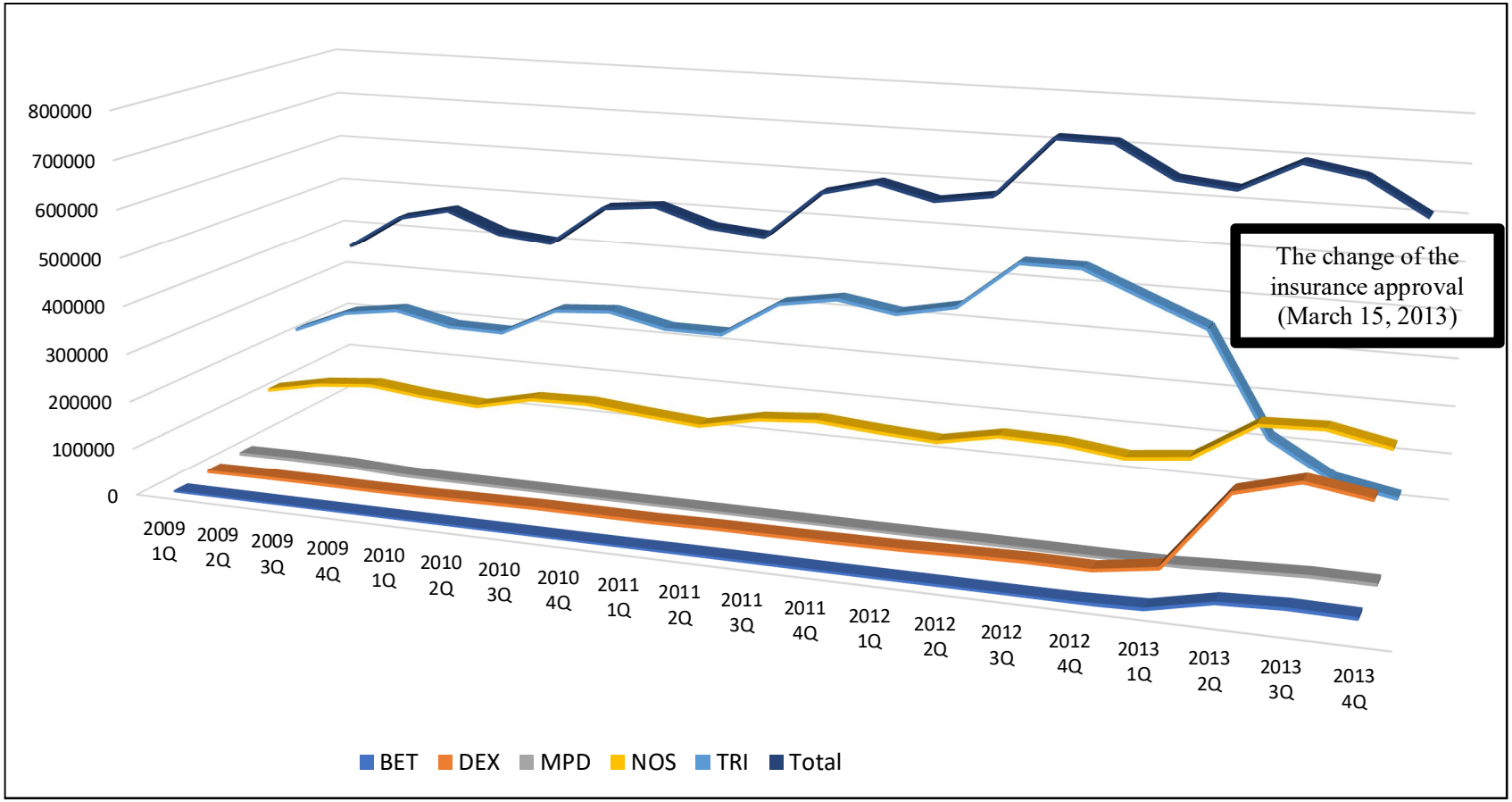

Figure 4. The number of injections increased yearly. National insurance changed steroid usage pattern after March 15, 2013: use of triamcinolone decreased while that of dexamethasone and steroid-free injections increased. Q, quarter; BET, betamethasone; DEX, dexamethasone; MPD, methylprednisolone; NOS, non-steroid, TRI, triamcinolone [27].

3.2. Demographic Characteristics of the Study Cohort and the Propensity Score-Matched Cohort

Table 9 showed the baseline demographic characteristics of the whole groups in the analysis. In the study cohort, 3,259,479 (36.2%) were male and 5,749,832 (63.8%) were female patients (mean age 63.4 ± 3.1 years). Their mean Charlson comorbidity index was 1.5 ± 0.9. Among all injections, the proportions of cervicothoracic injections, lumbosacral injections and caudal injections were 7.7%, 91.2%, and 1.2%, respectively. Particulate steroid use was more popular (53.8%) than non-particulate steroid use (9.9%) or non-steroid use (36.3%). Among local anesthetics, lidocaine was the most popular local anesthetics (70.0%) than mepivacaine (13.8%), bupivacaine (7.3%) or ropivacaine (2.8%). The proportion of patients using anti-thrombotic medications was 0.4%.

Table 10, 11, and 12 showed the baseline characteristics of people administered epidural injections in the study cohort and in the propensity score-mated cohort between comparison groups; injections with steroids versus without steroids (3,083,211 cases), injections with non-particulate steroids versus with particulate steroids (827,831 cases), and injections with non-particulate steroids versus non-steroid injections (779,067 cases), respectively. All standardized difference scores for the propensity score-matched cohorts were less than 0.1 (absolute value).

Table 9. Demographic characteristics of each group from 2010 to 2013 [27].

Characteristics		Non-particulate steroid				Particulate steroid				Non-Steroid		Total	
		Dexamethasone		Betamethasone		Triamcinolone		Methylprednisolone					
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Gender	Female	459,457	59.3	72,498	61.9	3,042,588	63.6	39,731	63.0	213,5558	65.3	5,749,832	63.8
	Male	315,344	40.7	44,623	38.1	1,741,356	36.4	23,334	37.0	1,134,822	34.7	3,259,479	36.2
Age	Mean, SD	61.6	±11.2	64.9	±13.2	62.8	±4.7	63.0	±13.2	64.8	±8.3	63.4	±3.1
	20-39	69,732	9.0	6,793	5.8	301,388	6.3	6,622	10.5	111,193	3.4	495,728	5.5
	40-59	268,081	34.6	34,316	29.3	1,468,671	30.7	22,514	35.7	886,273	27.1	2,679,855	29.7
	60-79	386,626	49.9	66,876	57.1	2,698,144	56.4	30,334	48.1	2,050,528	62.7	5,232,508	58.1
	80+	50,362	6.5	9,136	7.8	315,741	6.6	3,595	5.7	222,386	6.8	601,220	6.7
Injection	CTI	103,824	13.4	15,577	13.3	358,796	7.5	5,865	9.3	206,034	6.3	690,096	7.7
	LSI	660,905	85.3	97,562	83.3	4,367,741	91.3	53,984	85.6	3,034,913	92.8	8,215,105	91.2
	CB	10,072	1.3	3,982	3.4	57,407	1.2	3,216	5.1	29,433	0.9	104,110	1.2
CCI	Mean, SD	1.5	±1.1	1.3	±1.2	1.4	±1.0	1.7	±1.4	1.8	±1.1	1.5	±0.9
	0	200,001	25.8	31,388	26.8	1,379,076	28.8	14,190	22.5	811,054	24.8	2,435,709	27.0
	1	258,109	33.3	43,686	37.3	1,556,182	32.5	21,568	34.2	902,625	27.6	2,782,170	30.9
	2	154,930	20.0	25,181	21.5	904,665	18.9	10,532	16.7	660,617	20.2	1,755,925	19.5
	3	90,852	11.7	11,126	9.5	636,943	13.3	9,334	14.8	588,668	18.0	1,336,923	14.8
	4+	70,909	9.2	5,740	4.9	307,078	6.4	7,441	11.8	307,416	9.4	698,584	7.8
Combined anesthetics	Lidocaine	515,242	66.5	57,506	49.1	3,114,348	65.1	40,551	64.3	2,580,330	78.9	6,307,977	70.0
	Mepivacaine	72,831	9.4	20,262	17.3	645,832	13.5	3,532	5.6	500,368	15.3	1,242,825	13.8
	Bupivacaine	63,534	8.2	9,018	7.7	430,555	9.0	10,532	16.7	147,167	4.5	660,806	7.3
	Ropivacaine	45,713	5.9	11,244	9.6	153,086	3.2	757	1.2	39,245	1.2	250,045	2.8
	Others*	77,481	10.0	19,091	16.3	440,123	9.2	7,693	12.2	3,270	0.1	547,658	6.1
Blood thinners	Aspirin+Other antiplatelets†	3,099	0.4	468	0.4	14,352	0.3	312	0.5	9,782	0.3	28,013	0.3
	Warfarin+NOACs‡	775	0.1	117	0.1	4,784	0.1	60	0.1	3,970	0.1	9,706	0.1

	None	770,927	99.5	116,536	99.5	4,764,808	99.6	62,693	99.4	3,256,628	99.6	8,971,592	99.6
Total		774,801	8.6	117,121	1.3	4,783,944	53.1	63,065	0.7	3,270,380	36.3	9,009,311	100.0

*** "Others" includes procaine, mixed anesthetics, and no anesthetic. † "Other antiplatelets" include clopidogrel, Aggrenox, dipyridamole, triflusal, cilostazol, prasugrel, and ticagrelor. ‡ "Other anticoagulants" include heparin, enoxaparin, rivaroxaban, dabigatran, and apixaban. SD, standardized difference, CTI, cervicothoracic epidural injection; LSI, lumbosacral epidural injection; CB, cauda l block; CCI, Charlson comorbidity index.**

Table 10. Baseline characteristics of people in study cohort and in propensity based matched cohort between non-steroid and steroid injection groups [27].

		Non-Steroid	Steroid		Non-Steroid	Steroid	
		N=3,270,380	N=5,738,931	SD	N=3,083,211	N=3,083,211	SD
Gender	Female	2,135,558 (65.3)	3,614,274 (63.0)	0.048	1,997,582 (64.8)	1,992,556 (64.6)	0.006
	Male	1,134,822 (34.7)	2,124,657 (37.0)		1,085,629 (35.2)	1,090,655 (35.4)	
Age	Mean, SD	64.8 ± 8.3	62.6 ± 5.9	0.062	63.2 ± 8.8	63.1 ± 8.8	0.007
	20-39	111,193 (3.4)	384,535 (6.7)		110,471 (3.6)	110,718 (3.6)	
	40-59	886,273 (27.1)	1,793,582 (31.3)		878,499 (28.5)	879,733 (28.5)	
	60-79	2,050,528 (62.7)	3,181,980 (55.4)		1,887,203 (61.2)	1,883,749 (61.1)	
	80+	222,386 (6.8)	378,834 (6.6)		207,038 (6.7)	209,011 (6.8)	
Injection	CTI	206,034 (6.3)	484,062 (8.4)	0.081	204,139 (6.6)	205,619 (6.7)	0.004
	LSI	3,034,913 (92.8)	5,180,192 (90.3)		2,849,781 (92.4)	2,846,790 (92.3)	
	CB	29,433 (0.9)	74,677 (1.3)		29,291 (1.0)	30,801 (1.0)	
CCI	Mean, SD	1.8 ± 1.1	1.5 ± 1.0	0.075	1.5 ± 1.1	1.5 ± 1.1	0.004
	0	811,054 (24.8)	1,624,655 (28.3)		810,884 (26.3)	813,690 (26.4)	
	1	902,625 (27.6)	1,879,545 (32.8)		900,298 (29.2)	902,857 (29.3)	
	2	660,617 (20.2)	1,095,308 (19.1)		616,642 (20.0)	612,665 (19.9)	
	3	588,668 (18.0)	748,255 (13.0)		484,064 (15.7)	48,1690 (15.6)	
	4+	307,416 (9.4)	391,168 (6.8)		271,323 (8.8)	272,309 (8.8)	
Combined anesthetics	Lidocaine	2,580,330 (78.9)	3,727,647 (65.0)	0.097	2,426,610 (78.7)	2,426,549 (78.7)	0.005
	Mepivacaine	500,368 (15.3)	742,457 (12.9)		467,045 (15.1)	462,235 (15.0)	
	Bupivacaine	147,167 (4.5)	513,639 (9.0)		147,069 (4.8)	148,272 (4.8)	
	Ropivacaine	39,245 (1.2)	210,800 (3.7)		39,218 (1.3)	41,562 (1.3)	
	Others *	3,270 (0.1)	544,388 (9.5)		3,268 (0.1)	4,594 (0.1)	

Blood thinners	Aspirin+Other antiplatelets †	9,782 (0.3)	18,231 (0.3)	0.007	9,250 (0.3)	9,774 (0.3)	0.005
	Warfarin+NOACs‡	3,970 (0.1)	5,736 (0.1)		3,083 (0.1)	4,255 (0.1)	
	None	3,256,628 (99.6)	5,714,964 (99.6)		307,0878 (99.6)	3,069,182 (99.5)	

*** "Others" includes procaine, mixed anesthetics, and no anesthetic. † "Other antiplatelets" include clopidogrel, Aggrenox, dipyridamole, triflusal, cilostazol, prasugrel, and ticagrelor. ‡ "Other anticoagulants" include heparin, enoxaparin, rivaroxaban, dabigatran, and apixaban. SD, standardized difference, CTI, cervicothoracic epidural injection; LSI, lumbosacral epidural injection; CB, caudal block; CCI, Charlson comorbidity index.**

Table 11. Baseline characteristics of people in study cohort and in propensity based matched cohort between non-particulate and particulate steroid injection groups [27].

		Non-Particulate	Particulate steroid		Non-Particulate	Particulate steroid	
		N=891,922	N=4,847,009	SD	N=827,831	N=827,831	SD
Gender	Female	531,955 (59.6)	3,082,319 (63.6)	0.052	495,871 (59.9)	496,884 (60.0)	0.007
	Male	359,967 (40.4)	1,764,690 (36.4)		331,960 (40.1)	330,947 (40.0)	
Age	Mean, SD	61.2 ± 11.2	62.7 ± 6.8	0.073	61.4 ± 11.3	61.5 ± 11.3	0.008
	20-39	76,525 (8.6)	308,010 (6.4)		66,226 (8.0)	65,903 (8.0)	
	40-59	302,397 (33.9)	1,491,185 (30.8)		269,045 (32.5)	268,815 (32.5)	
	60-79	453,502 (50.8)	2,728,478 (56.3)		437,095 (52.8)	438,011 (52.9)	
	80+	59,498 (6.7)	319,336 (6.6)		55,465 (6.7)	55,102 (6.7)	
Injection	CTI	119,401 (13.4)	364,661 (7.5)	0.145	100,168 (12.1)	100,054 (12.1)	0.005
	LSI	758,467 (85.0)	4,421,725 (91.2)		714,418 (86.3)	714,651 (86.3)	
	CB	14,054 (1.6)	60,623 (1.3)		13,245 (1.6)	13,126 (1.6)	
CCI	Mean, SD	1.5 ± 1.2	1.5 ± 1.0	0.042	1.5 ± 1.2	1.5 ± 1.2	0.004
	0	231,389 (25.9)	1,393,266 (28.7)		218,547 (26.4)	218,688 (26.4)	
	1	301,795 (33.8)	1,577,750 (32.6)		278,151 (33.6)	278,068 (33.6)	
	2	180,111 (20.2)	915,197 (18.9)		164,738 (19.9)	164,655 (19.9)	
	3	101,978 (11.4)	646,277 (13.3)		97,684 (11.8)	97,799 (11.8)	
	4+	76,649 (8.6)	314,519 (6.5)		68,710 (8.3)	68,621 (8.3)	
Combined anesthetics	Lidocaine	572,748 (64.2)	3,154,899 (65.1)	0.031	533,123 (64.4)	533,321 (64.4)	0.004
	Mepivacaine	93,093 (10.4)	649,364 (13.4)		86,094 (10.4)	86,105 (10.4)	
	Bupivacaine	72,552 (8.1)	441,087 (9.1)		67,054 (8.1)	67,102 (8.1)	
	Ropivacaine	56,957 (6.4)	153,843 (3.2)		53,809 (6.5)	53,782 (6.5)	
	Others *	96,572 (10.8)	447,816 (9.2)		87,750 (10.6)	87,521 (10.6)	

Blood thinners	Aspirin+Other antiplatelets †	3,567 (0.4)	14,664 (0.3)	0.007	3,311 (0.4)	3,305 (0.4)	0.004
	Warfarin+NOACs‡	892 (0.1)	4,844 (0.1)		828 (0.1)	829 (0.1)	
	None	887,463 (99.5)	4,827,501 (99.6)		823,692 (99.5)	823,697 (99.5)	

*** "Others" includes procaine, mixed anesthetics, and no anesthetic. † "Other antiplatelets" include clopidogrel, Aggrenox, dipyridamole, triflusal, cilostazol, prasugrel, and ticagrelor. ‡ "Other anticoagulants" include heparin, enoxaparin, rivaroxaban, dabigatran, and apixaban. SD, standardized difference, CTI, cervicothoracic epidural injection; LSI, lumbosacral epidural injection; CB, caudal block; CCI, Charlson comorbidity index.**

Table 12. Baseline characteristics of people in study cohort and in propensity based matched cohort between non-particulate steroid and non-steroid injection groups [27].

		Non-Particulate	Non-Steroid		Non-Particulate	Non-Steroid	
		N=891,922	N=3,270,380	SD	N=779,067	N=779,067	SD
Gender	Female	531,955 (59.6)	2,135,558 (65.3)	0.063	493,149 (63.3)	493,135 (63.3)	0.007
	Male	359,967 (40.4)	1,134,822 (34.7)		285,918 (36.7)	285,932 (36.7)	
Age	Mean, SD	61.2 ± 11.2	64.8 ± 8.3	0.088	62.4 ± 11.3	62.4 ± 11.4	0.008
	20-39	76,525 (8.6)	111,193 (3.4)		42,313 (5.4)	42,372 (5.4)	
	40-59	302,397 (33.9)	886,273 (27.1)		252,887 (32.5)	253,217 (32.5)	
	60-79	453,502 (50.8)	2,050,528 (62.7)		430,858 (55.3)	430,359 (55.2)	
	80+	59,498 (6.7)	222,386 (6.8)		53,009 (6.8)	53,119 (6.8)	
Injection	CTI	119,401 (13.4)	206,034 (6.3)	0.164	88,102 (11.3)	88,211 (11.3)	0.006
	LSI	758,467 (85.0)	3,034,913 (92.8)		684,028 (87.8)	683,984 (87.8)	
	CB	14,054 (1.6)	29,433 (0.9)		6,937 (0.9)	6,872 (0.9)	
CCI	Mean, SD	1.5 ± 1.2	1.8 ± 1.1	0.103	1.5 ± 1.2	1.5 ± 1.2	0.004
	0	231,389 (25.9)	811,054 (24.8)		200,930 (25.8)	201,015 (25.8)	
	1	301,795 (33.8)	902,625 (27.6)		250,751 (32.1)	251,094 (32.2)	
	2	180,111 (20.2)	660,617 (20.2)		157,348 (20.2)	157,296 (20.2)	
	3	101,978 (11.4)	588,668 (18.0)		97,518 (12.5)	97,516 (12.5)	
	4+	76,649 (8.6)	307,416 (9.4)		72,820 (9.3)	72,146 (9.3)	
Combined anesthetics	Lidocaine	572,748 (64.2)	2,580,330 (78.9)	0.181	571,835(73.4)	571,832 (73.4)	0.005
	Mepivacaine	93,093 (10.4)	649,364 (13.4)		92,993 (11.9)	93,016 (11.9)	
	Bupivacaine	72,552 (8.1)	441,087 (9.1)		71,852 (9.2)	71,998 (9.2)	
	Ropivacaine	56,957 (6.4)	153,843 (3.2)		39,119 (5.0)	39,038 (5.0)	
	Others *	96,572 (10.8)	447,816 (9.2)		3,268 (0.4)	3,183 (0.4)	
Blood thinners	Aspirin+Other antiplatelets †	3,567 (0.4)	14,664 (0.3)	0.007	3,495 (0.4)	3,498 (0.4)	0.005

	Warfarin+NOACs‡	892 (0.1)	4,844 (0.1)	891 (0.1)	891 (0.1)
	None	887,463 (99.5)	4,827,501 (99.6)	823,692 (99.5)	823,697 (99.5)

*** "Others" includes procaine, mixed anesthetics, and no anesthetic. † "Other antiplatelets" include clopidogrel, Aggrenox, dipyridamole, triflusal, cilostazol, prasugrel, and ticagrelor. ‡ "Other anticoagulants" include heparin, enoxaparin, rivaroxaban, dabigatran, and apixaban. SD, standardized difference, CTI, cervicothoracic epidural injection; LSI, lumbosacral epidural injection; CB, caudal block; CCI, Charlson comorbidity index.**

3.3. Incidence Rates of Neurological Complications and Comparisons between Steroid Use Patterns

We included gender, age, level of spinal injection, Charlson comorbidity index, local anesthetics, and blood thinners in the final propensity score model. We estimated incidence rates of the neurological complications after epidural injections with steroids versus those without steroids were 1.48 per 100,000 person-days (95% CI 1.25–1.65) versus 0.86 per 100,000 person-days (95% CI 0.66–1.30), respectively. In addition, we calculated incidence rates of the neurological complications with injections with particulate steroids versus non-particulate steroids were 1.73 per 100,000 person-days (95% CI 1.41–1.95) versus 0.90 per 100,000 person-days (95% CI 0.43–1.47). In particular, the incidence rate of neurological complications with particulate steroid injections (4.58 per 100,000 person-days, 95% CI 2.82–5.25) is higher than that with non-particulate steroid injections at the cervicothoracic level (0.84 per 100,000 person-days, 95% CI 0.02–2.80, Figure 5).

		Number of events	Crude HR (95% CI)	Adjusted HR (95% CI) *	Incidence rate per 100,000 person-days (95% CI)
Without steroid	Overall	28†	1	1	0.86 (0.66-1.30)
Steroid	Overall	85	1.72 (0.96-2.50)	1.71 (0.96-2.49)	1.48 (1.25-1.65)
Without steroid	CTI	2	1	1	0.97 (0.34-3.61)
Steroid	CTI	15	3.20 (0.55-12.03)	3.20 (0.56-12.02)	3.10 (1.98-4.09)
Without steroid	LSI	26	1	1	0.82 (0.61-1.26)
Steroid	LSI	70	1.64 (0.89-2.51)	1.65 (0.90-2.50)	1.35 (1.12-1.53)
Non-particulate steroid	Overall	8‡	1	1	0.90 (0.43-1.47)
Particulate steroid	Overall	77§	1.92 (0.96-4.53)	1.92 (0.97-4.52)	1.73 (1.41-1.95)
Non-particulate steroid	CTI	1	1	1	0.84 (0.02-2.80)
Particulate steroid	CTI	14	4.98 (1.01-262.38)⁋	4.98 (1.01-262.35)⁋	4.58 (2.82-5.25)
Non-particulate steroid	LSI	7	1	1	0.92 (0.15-1.26)
Particulate steroid	LSI	63	1.54 (0.96-11.00)	1.55 (0.96-11.00)	1.42 (1.19-1.71)
Non-Particulate steroid	Overall	8	1	1	0.90 (0.43-1.47)
Without steroid	Overall	28	0.96 (0.45-3.02)	0.97 (0.46-3.01)	0.86 (0.66-1.30)
Non-Particulate steroid	CTI	1	1	1	0.84 (0.02-2.80)
Without steroid	CTI	2	1.15 (0.12-180.50)	1.15 (0.14-180.47)	0.97 (0.34-3.61)
Non-Particulate steroid	LSI	7	1	1	0.92 (0.15-1.26)
Without steroid	LSI	26	0.89 (0.48-8.39)	0.89 (0.49-8.39)	0.82 (0.61-1.26)

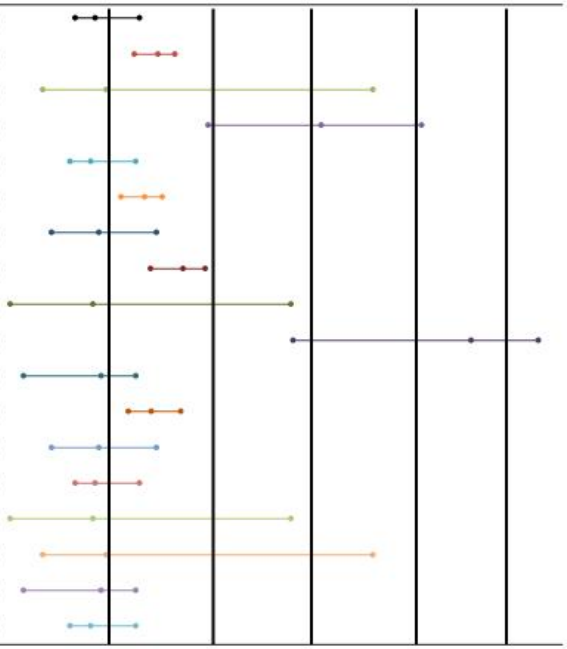

Figure 5. Incidence rates and hazard ratios for neurological complications among patients who received at least one epidural injection from 2010 to 2013. The incidence rate of neurological complications with particulate steroid injections is higher than that with non-particulate steroid injections at the cervicothoracic level. * Adjusted for age, gender, Charlson comorbidity index, anesthetics, and blood thinner in follow up periods. Lists of neurological complications: † 15 Cerebrovascular diseases, 2 Vascular syndromes of brain in cerebrovascular diseases, 9 Disease of spinal cord (Myelopathy NOS), 1 Paraplegia/Tetraplegia, 1 Other paralytic syndromes, ‡ 5 Cerebrovascular diseases, 2 Disease of spinal cord (Myelopathy NOS), 1 Other paralytic syndromes, § 36 Cerebrovascular diseases, 5 Vascular syndromes of brain in cerebrovascular diseases, 23 Disease of spinal cord (Myelopathy NOS), 4 Neurogenic bladder due to cauda equine syndrome, 3 Hemiplegia, 4 Paraplegia/Tetraplegia, 1 Other paralytic syndromes, 1 Other sudden death (cause unknown) ⁋ *p*-value<0.05 statistically significant CI, confidential interval; HR, Hazard ratio; CTI, cervicothoracic epidural injection; LSI, lumbosacral epidural injection [27].

For comparison of neurological complication rates between steroid injections and non-steroid injections, we estimated the adjusted hazard ratios (aHR) after epidural injections. The aHR of epidural injections with steroids compared to those of epidural injections without steroid was 1.71 (95% CI 0.96–2.49). Compared to epidural injections with non-particulate steroids, the aHR of epidural injections with particulate steroids was 1.92 (95% CI 0.96–4.53). The aHR of epidural injections with particulate steroids at the cervicothoracic level was significantly higher: 4.98 (95% CI 1.01–262.35). However, the aHR of epidural injections without steroid compared to that of epidural injections with non-particulate steroids was 0.97 (95% CI 0.46–3.01). We could not get statistically meaningful results when we extended exclusion criteria (i.e. extending washout periods) or inclusion criteria (i.e. including cases of neurological complications up to 7 post-procedural days) (Figure 6).

		No of events	Crude HR (95% CI)	Adjusted HR (95% CI) [a]	Incidence rate per 100,000 person-days (95% CI)
Washout period for 2 years	Without steroid	22	1	1	0.96 (0.63-1.31)
	Steroid	71	1.39 (0.87-2.52)	1.39 (0.88-2.51)	1.33 (1.14-1.59)
Washout period for 2 years	Non-particulate steroid	7	1	1	0.93 (0.41-1.52)
	Particulate steroid	64	1.90 (0.94-4.78)	1.90 (0.94-4.77)	1.77 (1.43-1.96)
Post-procedural complications within 3 days	Without steroid	39	1	1	1.19 (0.83-1.46)
	Steroid	92	1.34 (0.93-2.41)	1.34 (0.94-2.41)	1.60 (1.36-2.00)
Post-procedural complications within 3 days	Non-particulate steroid	10	1	1	1.12 (0.67-1.71)
	Particulate steroid	82	1.51 (0.81-3.00)	1.51 (0.82-3.00)	1.69 (1.38-2.01)
Post-procedural complications within 7 days	Without steroid	41	1	1	1.25 (0.81-1.45)
	Steroid	107	1.49 (0.91-2.10)	1.49 (0.92-2.10)	1.86 (1.31-1.71)
Post-procedural complications within 7 days	Non-particulate steroid	12	1	1	1.35 (0.70-1.75)
	Particulate steroid	95	1.45 (0.99-3.20)	1.45 (0.99-3.19)	1.96 (1.73-2.24)

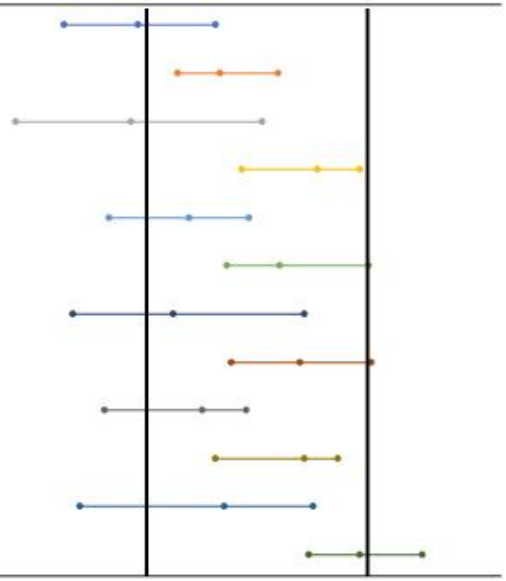

Figure 6. The sensitivity analysis yielded no statistically significant results. *Adjusted for age, gender, Charlson comorbidity index, anesthetics, and blood thinner in follow up periods. † *p*-values < 0.05 were considered statistically significant. CI, confidence interval; HR, hazard ratio [27].

4. Discussion

4.1. Study Summary

In the present study, we determined the incidence of major neurological complications following epidural injections. We found that these complications were rare, but that steroid usage, and especially that of particulate steroids, increased the risk of neurological complications following cervicothoracic steroid injections. Neurological complication rates did not differ in patients who underwent non-particulate steroid and non-steroid injection procedures.

4.2. Comparison to Previous Studies

Several retrospective studies previously reported that epidural steroid injections were reasonably safe because they were associated with complication rates of less than 3% and with no serious neurological complications [28, 29]. However, these previous studies were limited in their ability to apply to the general population because they used only retrospective single-center data. Case series and surveys reported infections, hypotension, seizure, stroke, spinal cord injury, and even death occurred after epidural injections [30]. However, complications were likely underreported due to medicolegal problems because epidural steroid use is still off-label in many countries [14, 31].

Scanlon et al. conducted one anonymous survey of physicians in the American Pain Society. While only 287 of the 1,340 physicians in the Society responded, 78 cases of serious neurological complications, including 16 vertebrobasilar brain infarcts, 12 cervical spinal cord infarcts, 2 brain and spinal infarcts, and 13 deaths were reported [15]. Most cases occurred after cervical injections, but some neurological complications also occurred after lumbar injections [32, 33]. Since 2000, several catastrophic events have been reported after nerve root blocks or epidural injections. All cervical cases occurred within a few minutes after injections (Table 12) [34-42]. In cervical cases, most cases except for one (in which, following contrast injection, the patient developed cortical blindness and the procedure was aborted) employed particulate steroids (triamcinolone or methylprednisolone) [41]. Case reports of spinal cord infarctions or injuries after lumbar epidural injection or nerve root block have also been reported (Table 13) [32, 33, 43-54]. Only recently, one case of dexamethasone transforaminal injection [43] was reported, with other published cases occurring after particulate steroid injections [32, 33, 43, 45-54].

Subsequently, the FDA began evaluating serious major neurological adverse events following spinal steroid injections by collecting reports from the FAERS. Between 1997 and 2014, a total of 90 serious complications were identified [14]. The FDA excluded cases associated with fungal meningitis due to contamination of compounded steroids [55] and issued a warning that epidural steroid injection procedures might increase the incidence of serious neurological complications. However, this warning included all

types of corticosteroids, and did not specify incidence rates for each corticosteroid [17].

Given the large number of epidural injections performed, there is an urgent need to establish a valid estimate of the incidence of neurological complications [14]. However, we were unable to identify any previous population-based studies that estimated complication rates following these procedures. If we assume that epidural anesthesia is one of many possible epidural procedures, some hints about complication rates with an epidural approach may be gleaned from previous claim data. For instance, one Finnish study using 2000-2009 closed claim data found that fatalities occurred after 1:62,000 epidurals for acute pain relief, after 1:12,000 epidurals for chronic pain relief, and after 1:144,000 epidurals for labor-related pain [56]. This study also reported that most patients suffering from serious complications were elderly and had comorbidities, irrespective of the neuro-axial method used. A comprehensive prospective UK study also reported 'pessimistic' (worst case) and 'optimistic' (best case) outcome incidences; all cases where the cause was judged to be unlikely were excluded from the optimistic analysis, which yielded an incidence of permanent injury of 2.0 (confidential interval [CI] 1.1-3.3) per 100,000 cases. The pessimistic outcome incidence was 4.2 (CI 2.9-6.1) [57]. In addition, one Chinese study evaluated continuous epidural anesthesia in 5083 cases at a Chinese hospital. Sixty-nine (1.36%) patients in this study experienced major complications, and one (0.02%) experienced permanent sequalae [58]. While most epidural anesthesia does not need steroids, complications after epidural steroid injection procedures are rare but do occur. However, serious neurological complications from epidural injections were rare in the present study as compared to previous data from epidural anesthesia cases.

Table 13. Summary of previous neurological complications after cervical epidural injections and selective nerve root blocks.

Author/year	Image-guided	Procedure	Age/Sex	Surgical history	Injectate	Needle	Event
Brouwers et al. [42]/2001	FLU*	Right C6-7 NRB	48/Male	No information	0.2 ml Iotrolan+0.5 ml triamcinolone +0.5 ml 0.5% bupivacaine	22 G spinal	C3 quadriplegia (spinal cord infarct)
Rozin et al. [40]/2003	FLU	Left C7 NRB	44/Female	No information	Unknown amount Omnipague 300 + 80 mg methylprednisolone + 0.75% bupivacaine (Total 3 ml)	25 G 3.5inch Quincke	Death (brainstem hemorrhage)
McMillan and Crumpton [40]/2003	FLU	Left C5–C6 TFEI	54/Male	C3-C7 decompression and C6-7 fusion	2 ml iopamidol	22 G 6cm spinal	Cortical blindness over 3 weeks (edema of occipital cortex)
Tiso et al. [38]/2004	FLU	Right C5–C6 TFEI	48/Female	No information	2 ml Isovue M 200 + 80 mg triamcinolone + 2 ml 0.25% bupivacaine	25 G 2inch Quincke	Cerebellar infarct/Death
Karasek and Bogduk [39]/2004	FLU	Right C6–C7 TFEI	55/Female	No information	Unknown amount contrast + 0.8 ml 2% lidocaine	Unknown gauge	Paralysis of extremities for 20 min
Ludwig and Burns [37] /2005	FLU	Left C6 TFEI	53/Male	no Hx of surgery	Unknown amount Omnipaque-240 + 0.75cc 0.75 bupivacaine and 0.75 cc triamcinolone	25 G 2.5inch	C4 quadriplegia (spinal cord infarction)
Muro et al. [36]/2007	FLU	Left C5-6, C6-7 TFEI	72/Female	C4-5 C5-6 ACDF	Unknown amount Isovue + 40mg methylprednisolone and 0.7 ml 0.5% bupivacaine	25G 3.5inch spinal	C3 quadriplegia (spinal cord infarction)
Han M [35]/2008	FLU	C7-T1 ILEI	46/Female	C5-6 ACDF	2 ml Iopamiro-300 +20mg triamcinolone+0.125% levobupivacaine (toal 6.5ml)	18 G Tuohy	Quadriparesis (worsening C7 cervical myelopathy)
Moon and Kwon [34]/2017	FLU	Left C6-7 TFEI	49/Male	no Hx of surgery	20mg triamcinolone+ 2 ml 0.125% levobupivacaine	Unknown	C2 quadriplegia (Spinal cord infarction)

***FLU, fluoroscopy-guided; NRB, nerve root block; TFEI, transforaminal epidural injection; ILEI, interlaminar epidural injection; ACDF, anterior cervical discectomy and fusion; G, gauge.**

Table 14. Summary of previous neurological complications after lumbar epidural and selective nerve root blocks.

Author/year	Image-guided	Procedure	Age/Sex	Surgical history	Injectate	Needle	Event
Lee and Kim [54]/2000	FLU*	L3-4 ILEI	70/Female	No information	80mg Triamcinolone + 6 ml 1.5% lidocaine	18 G Tuohy	Cardiac/respiratory arrest for 5min, Pneumocephalus
Houten and Errico [53]/2002	FLU	Right L3–L4, L4–L5 TFEI	64/Female	L4-5 laminectomy	1 ml Monipague + 12 mg betamethasone + 3 ml 0.25% bupivacaine	25 G spinal	L1 paraplegia (spinal cord edema)
	CT	Left L3–L4 TFEI	51/Female	L5-S1 fusion with pedicle screw instrumentation	0.2 ml Isovue 300+40 mg methylprednisolone + 1 ml 1% lidocaine	20 G spinal	Low thoracic paraplegia (spinal cord edema)
	CT	Left L5-S1 TFEI	42/Male	Lumbar laminotomy and microdiscectomy	Small amount contrast + 40 mg methylprednisolone + 1 ml 1% lidocaine	22 G spinal	T10 paraplegia (spinal cord infarct)
Huntoon and Martin [52]/2004	FLU	Left L1-L2 TFEI	64/Male	Multiple spine surgeries (L2 fusion)	1 ml iopamidol + 40 mg triamcinolone + 5 ml 0.125% bupivacaine	25 G and 22 G 3.5inch Quincke	T10 paraplegia (spinal cord infarct)
Glaser and Falco [51]/2005	FLU	Left T12-L1 TFEI	67/Female	T12 compression fracture	3 ml 1% ropivacaine + 50 mg triamcinolone	22 G 3.5inch spinal	T5 Paraplegia (spinal cord infarct)
Somayaji et al.[50]/2005	CT	Left L2–L3 NRB	71/Female	no Hx of surgery	Unknown amount Isovue-300 + 40 mg triamcinolone + 1 ml 0.5% bupivacaine	21 G spinal	L2 paraplegia (spinal cord infarct)
Tripathi et al. [49]/2005	FLU	T11-12 ILEI	62/Male	No information	3 mL of 1.5% lidocaine with epinephrine +triamcinolone (40 mg) in 10 mL of bupivacaine (0.125%)	18 G Tuohy	T9 paraplegia-Intra-cord injection
Quintero et al.[48] 2006	FLU	Left L4-5 TFEI	40/Male	no Hx of surgery	125mg hydrocortisone	20G spinal	T12 paraplegia (spinal cord infarct)
Kennedy et al. [33]/2009	FLU	Left L3-4 TFEI	83/Female	no Hx of surgery	Unknown amount Isovue-300 + 6mg/c1cc betamethasone acetate + 0.75% 1cc bupivacaine	26 G 3.5inch spinal	L1 paraplegia (spinal cord infarct)

	CT	Right L3-4 TFEI	79/Male	Lumbar fusion	2 ml Omnipaque + 160mg methylprednisolone + 6 ml 0.375% Marcaine	22 G spinal	T9 paraplegia (spinal cord infarct)
Lyders and Morris [32]/2009	FLU	Right L2-3 TFEI	55/Female	No information	2 ml contrast + total 1 ml (triamcinolone + 0.25% bupivacaine)	22G spinal	Spinal cord infarction (Right L2 segmental artery occlusion -No visualization of artery of Adamkeiwicz)
Wybier M et al.[47]/2010	FLU	Left L5-S1 TFEI	46/Male	Left L5-S1 disc excision	Unknown amount Prednisolone acetate	No information	T10 paraplegia (spinal cord infarct)
	FLU	Left L1-2 ILEI	43/Male	Bilateral L2-S1 laminectomy, L4-5 posterolateral fusion	Unknown amount contrast +Prednisolone acetate	No information	T12 paraplegia (spinal cord infarct)
	FLU	Left L3-4 TFEI	78/Female	Bilateral L3-5 laminectomy, partial Rt L4-5 facet arthrectomy	Unknown amount contrast +Prednisolone acetate	No information	T12 paraplegia (spinal cord infarct)
	FLU	Right L5-S1 TFEI	63/Male	no Hx of surgery	Unknown amount Prednisolone acetate	No information	Transient paraplegia followed by long-lasting severe right L5 deficit
	FLU	Left L4-5 juxta-zygopophyseal	64/Male	Bilateral L2-5 laminectomy	Unknown amount Prednisolone acetate +local anesthetics	No information	T12 paraplegia (spinal cord infarct)
Tackla et al.[46]/2012	FLU	Left L4-5 TFEI	47/Male	L4-5 laminectomy and discectomy	No information	No information	Conus medullaris syndrome
Gharibo CG et al.[45]/2016	FLU	Right L4 TFEI	60/unknown gender	No information	2 ml contrast + 1.5 ml 4mg/ml Dexamethasone + 1.5 ml normal saline	22G spinal	T12-L1 Conus medullaris infarction
Ghaly et al. [44]/2018	FLU	Right L5-S1 TFEI	49/Male	No information	3 ml contrast +10mg dexamethasone + 1 ml 1% lidocaine	No information	Immediate foot drop L5-S1 denervation
Wang et al.[43]/2018	No image-guided	Caudal injection	52/Male	No information	30 ml normal saline + 35mg 0.5% lidocaine and 100mg prednisolone	No information	Spinal cord infarction

***FLU, fluoroscopy-guided; CT, computed tomography-guided; NRB, nerve root block; TFEI, transforaminal epidural injection; ILEI, interlaminar epidural injection; G, gauge.**

4.3. Mechanism of Neurological Complications

Several mechanisms may explain neurological complications following epidural steroid injection [30]. For example, the epidural technique itself may result in neurological complications due to direct needle injury or needle-induced vasospasm. The American Society of Anesthesiologists Closed Claims Study Group previously reported cases of spinal cord injuries caused by direct needle trauma [59]. This direct trauma is associated with cervical level injections or deep sedation during procedures [59]. In addition, patients with a history of spinal surgery may face an increased complication risk because of changes in the structural or vascular anatomy of the epidural space [52]. Furthermore, arterial dissections, steroid-induced vasospasms in the vascular endothelium, and direct vascular perforations may also result in neurological complications [40, 51, 60]. Finally, the neurotoxicity of the preservatives used in corticosteroid formulations may also cause lasting neurological damage [61].

Epidural steroids have systemic side effects that depend on both their dose and on the number of injections administered. These effects may include down-regulation of the hypothalamic pituitary axis and of the immune system [62]. In particular, steroids modulate both the innate and adaptive immune systems by inhibiting neutrophil migration to infection sites and macrophage/monocyte functionality, as well as reducing immunoglobulin production in the plasma [63, 64]. One study reported that vaccinated patients who received steroid injections were at increased risk for developing influenza relative to vaccinated patients who did not receive steroid injections [65]. Severe infections were rare and included meningitis, epidural abscesses, osteomyelitis, and discitis [66].

Animal and pharmacological studies have suggested that particulate steroid embolization due to inadvertent intra-arterial injection may underlie strokes or spinal cord infarctions [23, 67-70]. For instance, animal studies have revealed that direct injection of particulate steroids into the vertebral artery causes irreversible neurological damage, whereas soluble steroid injection does not [67, 69, 70]. Given this existing scientific evidence, an expert multi-disciplinary working group concluded that particulate steroids should not be used in therapeutic cervical transforaminal injections [20].

In addition, we performed sensitivity analysis to figure out whether we could get any statistically significant results if we changed our inclusion criteria (Figure 6). When we extended washout period for 2 years, we could not see any meaningful results. Furthermore, we analyzed our data by extending post-procedural neurological complications until 3 days or 7 days after epidural injections. Interestingly, we could not find out statistically significant results. We believed these results could support embolization is the most important etiology to cause neurological complications. This is because embolization lead to acute neurological complications rather than delayed neurological complications, compared to other possible etiologies.

4.4. Characteristics of Corticosteroids in Epidural Injections

Often, corticosteroids and local anesthetics are administered together during epidural injections. Injectable corticosteroids are often classified as soluble non-particulate or insoluble particulate steroids. Most injectable steroids contain esters, rendering them water-insoluble and lending them longer half-lives, as they require hydrolysis to activate. On the other hand, sodium phosphate renders steroids water soluble. For instance, sodium phosphate hastens the effect of dexamethasone and betamethasone, but at a cost to their duration of action [71]. Steroid preparations also have different tendencies to aggregate into larger particles depending on drug concentrations, co-administered preservatives, drug vehicles, and combined local anesthetic use (Table 12) [72].

Laboratory studies have found that particulate steroids may aggregate to become larger than red blood cells. Microscopic analyses have demonstrated that these aggregates can further occlude small arterioles [23, 68]. For instance, intra-arterial administration of particulate steroids occluded microvascular blood flow in the arterioles and venules in the mouse cremaster muscle due to red blood cell aggregation. Interestingly, intra-arterial dexamethasone did not cause the same occlusion effect [73].

Micro and macroscopic studies have further demonstrated that ropivacaine crystallizes at a specific pH level, even when soluble corticosteroids such as dexamethasone or betamethasone sodium phosphate are also administered, whereas lidocaine does not precipitate with some steroids, such as triamcinolone [74]. Given this, the combined effect of local anesthetics and steroids may be another important factor. In the present study, we found that ropivacaine was the fourth most popular anesthetic, though it was used in only 2.8% of all injection procedures. Furthermore, we found no evidence that ropivacaine increased neurological complication risk in the present study.

It is also important to consider the long-term safety of repeated epidural injections. One study in patients with spinal stenosis reported that most subjects treated with dexamethasone and betamethasone recovered normal cortisol levels three weeks post-injection. However, 20.3% of patients treated with methylprednisolone or triamcinolone had greater than 50% decreases from baseline cortisol levels by

three weeks [75].

Despite some convincing evidence for the safety profile of non-particulate steroids, there remains debate about whether this is offset by potentially increased particulate steroid effectiveness in lumbar transforaminal epidural injections [13, 76]. The relevant literature is somewhat divided, with no demonstrated differences in pain reduction or physical disability between particulate and non-particulate steroids in some studies [76, 77]. In other studies, including a recent meta-analysis, particulate steroids offer no increased benefit for pain reduction over non-particulate steroids [78]. If particulate and non-particulate steroids do indeed offer equal efficacy, steroid selection should then be based on associated risk [79.80]. Furthermore, a recent meta-analysis demonstrated that epidurally-administered local anesthetics alone were effective for reducing low back and radicular pain [81]. Thus, epidural injections with local anesthetics alone may be a viable option for treating pain in high-risk patients who are more likely to develop steroid-induced adverse effects.

To avoid neurological complications, physician procedural experience and expert knowledge of fluoroscopic anatomy and procedural risks are critical [15]. The results presented here agree with previous studies that have also demonstrated that cervicothoracic injections are associated with increased risk relative to lumbosacral injections [15]. However, of note to clinicians, lumbar injections may also cause spinal cord infarctions and injuries [82]. Furthermore, individual patient factors should also be considered. For instance, there may be some benefit to withholding anti-coagulants and anti-platelet drugs 2–5 days before injection procedures [83]. However, this is somewhat unclear, as a recent study reported that the administration of continuing anticoagulants in patients undergoing interventional pain procedures did not increase risk for hemorrhagic complication, fatal stroke, or myocardial infarction [84]. Furthermore, a history of spinal surgery could increase complications because of postoperative anatomical alterations [52]. Physicians should consider these possible contributors to risk and prepare strategies to promptly manage potential complications [30].

Table 15. Summary of Properties of Various Steroid Preparations [85].

Steroid	Equivalent potency (mg)	Solubility*	Maximum Particle Size (μm) †	Particles>10 μm†	Particle Aggregation†	Crystallization with local anesthetics
Methylprednisolone acetate	4	0.001‡	>500	45	Few	Unknown
Triamcinolone acetonide	4	0.0002‡	>500	45	Extensive	No crystallization with lidocaine, bupivacaine or ropivacaine
Betamethasone sodium phosphate	0.75	Freely soluble	500	35	Some	Crystallization with bupivacaine and ropivacaine
Dexamethasone sodium phosphate	0.75	Freely soluble	0.5	0	None	Crystallization with ropivacaine

* Information obtained from package inserts for each commercial product.

†Maximal size of a red blood cell is approximately 10 μm.

‡ Value is percent wt/vol.

4.5. Study Limitations

Despite its advantages, the present study has some limitations which warrant discussion. In the real-world, particulate steroid injections are significantly more popular than non-particulate steroids and non-steroid injections. Given this, we used propensity score matching to ensure that differences between treatment groups were comparable. However, propensity score matching cannot adjust for unknown variables [25].

Moreover, insurance claim data lacked information about physician experience/skills, patient socioeconomic status, severity of the patient's condition (i.e. National Institutes of Health Stroke Scale or American Spinal Injury Association Impairment Scale scores), or pain severity. In addition, if patients had neurological complications or underwent spinal surgeries before 2009, we could not exclude them because we did not have information before 2009. However, we determined that a one-year period was sufficient to exclude those cases because most patients with neurological complications required continuous medical care rather than new care after one year. Furthermore, some epidural procedures, such as epidural neurolysis, were not covered by national insurance and as such were not included because insurance claim data did not include this procedural data.

A further limitation of the present study was that inpatient insurance claim data included only discharge diagnoses and not admission diagnoses. Therefore, insurance claim data may have been miscoded or not coded at all. However, a previous validation study reported an overall positive predictive value of the diagnoses of over 83.4% in patients admitted to the hospital [86]. Importantly, procedure codes from the HIRA dataset did not allow us to differentiate between interlaminar and transforaminal epidural injections. The multi-society pain group recommended the use of non-particulate steroids for cervical transforaminal epidural injections. Though our study did not differentiate between approach types, our results did demonstrate that non-particulate steroid injections were as safe as non-steroid injections at the cervicothoracic level. Further studies are required to investigate the safety and efficiency of cervical transforaminal injections versus interlaminar injections using non-particulate steroids.

Despite these limitations, our study is the first to estimate incidence rates of acute neurological complications in the real world using a large national database, which includes most patients who underwent these injections. Given this benefit, the present study is robust and has good generalizability. The present study also revealed that changes in insurance approvals do in fact influence practice patterns, as evidenced by the fact that non-steroidal and non-particulate steroid injections replaced particulate steroid injections after March of 2013.

5. Conclusion

The present study investigated the incidence of acute neurological complications after epidural injections. However, the long-term adverse effects of these procedures should be investigated further. At present, the HIRA only allows for less than 15 epidural injections within a year or three times within a two-week period in South Korea. The spine intervention society recommends an interval between injections of at least 2-3 weeks and no greater than two repeat injections in selected patients within an initial 6-month period [87]. However, there is no clinical data on long-term complication rates (i.e. infection) or safe annual maximum injection frequencies. Therefore, future studies should focus on long-term benefit and risk.

In conclusion, the incidence of neurological complications after particulate steroid injections (1.73 per 100,000 person-days, 95% CI 1.41–1.95) is higher than that after non-particulate steroid injections (0.90 per 100,000 person-days, 95% CI 0.43–1.47). In particular, the incidence rate of neurological complications with particulate steroid injections at the cervicothoracic level (4.58 per 100,000 person-days, 95% CI 2.82–5.25) is higher than that with non-particulate steroid injections at the cervicothoracic level (0.84 per 100,000 person-days, 95% CI 0.02–2.80). Additionally, injections with non-particulate steroids should be considered as safe as non-steroid injections. Acute neurological complications were rare in the present study, though some patients experienced significant long-term sequalae. Physicians should consider these outcomes and should be particularly cautious when performing epidural procedures at the cervicothoracic level.

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국문 초록

배경 및 목적: 경막외 주사는 요통과 경추통에 널리 사용되는 시술로 주사에 사용되는 스테로이드제제의 안전성에 대한 논란이 있어 왔다. 본 연구에서는 경막외 주사의 신경학적 합병증 발생률을 사용되는 스테로이드 제제의 차이에 따라 비교하기 위하여 건강보험심사평가원 보험청구자료를 이용한 후향적 코호트연구를 수행하였다.

연구 방법: 건강보험심사평가원 자료를 이용하여 우리나라에서 2009 년부터 2013 년까지 척추 관련 상병으로 경막외 주사나 선택적 신경근 차단술을 한 번 이상 시행 받은 환자들을 대상으로 선정하였다. 2009 년에 뇌경색, 척수경색, 마비, 시각손실 등의 신경학적 합병증으로 1 회 이상 입원치료나 2 회 이상 외래치료를 받은 환자와 척추 수술을 받은 환자는 제외하였다. 2010 년도부터 경막외 주사나 선택적 신경근 차단술을 시행받은 환자 중에서 시술 후 24 시간 이내에 병원에 입원하여 신경학적 합병증으로 입원치료받은 환자를 확인하였다. 그 환자들의 찰슨동반질환지표점수, 나이, 성, 사용된 국소마취제, 항혈전제 등을 공변량으로 확인한 후, 성향점수를 산출하였다. 이후 스테로이드제제를 사용하지 않은 경우와 스테로이드제제를 사용한 경우, 스테로이드제제를 사용한 경우에는 비입자성 스테로이드제제를 사용한 경우와 입자성 스테로이드제제를 사용한 경우의 신경학적 합병증의 발생률을 각각 산출하였다. 이후에 스테로이드제제를 사용하지 않은 경우와 스테로이드제제를 사용한 경우, 비입자성 스테로이드제제를 사용한 경우와 입자성 스테로이드제제를 사용한 경우, 비입자성 스테로이드제제를 사용한 경우와 스테로이드 제제를 사용하지 않은 경우로 성향점수를 이용한 짝짓기를 통한 코호트연구를 수행하여 상대위험도와 95% 신뢰구간을 추정하였다.

연구 결과: 연구 기간 동안 가장 많이 사용된 스테로이드제제는 트리암시놀론이었다 (53.8%). 그러나 2013 년 3 월 15 일 보험고시 변경 이후, 덱사메타손을 사용하거나 스테로이드를

사용하지 않는 경막외 주사의 분율이 급증한 것을 확인할 수 있었다. 스테로이드제제를 사용한 경우와 사용하지 않은 경우 신경학적 합병증 발생률은 각각 100,000 인-일당 1.48 (95% 신뢰구간 1.25-1.65)와 0.86 (95% 신뢰구간 0.66-1.30)이었다. 입자성 스테로이드제제를 사용한 경우와 비입자성 스테로이드제제를 사용한 경우 신경학적 발생률은 각각 100,000 인-일당 1.73 (95% 신뢰구간 1.41-1.95)와 0.90 (95% 신뢰구간 0.43-1.47)이었다. 스테로이드제제를 사용한 경우 스테로이드제제를 사용하지 않은 경우에 비해 신경학적 합병증 발생의 상대위험도는 1.71 (95% 신뢰구간 0.96-2.49)로 나타났다. 입자성 스테로이드제제를 사용한 경우 비입자성 스테로이드제제를 사용한 경우에 비하여 신경학적 합병증 발생의 상대위험도는 1.92 (95% 신뢰구간 0.96-4.53)로 나타났다. 경흉추 레벨에서는 입자성 스테로이드제제를 사용한 경우 비입자성 스테로이드제제를 사용한 경우에 비해 신경학적 합병증 발생의 상대위험도는 4.98 (95% 신뢰구간 1.01-262.35)로 나타났다. 비입자성 스테로이드제제를 사용한 경우와 스테로이드제제를 사용하지 않은 경우를 비교한 상대위험도는 0.97 (95% 신뢰구간 0.46-3.01)로 나타났다.

결론: 본 연구결과, 경흉추 레벨의 입자성 스테로이드제제를 사용한 경막외 주사의 신경학적 합병증의 발생률이 비입자성 스테로이드제제를 사용한 경우보다 높은 것을 확인하였다. 그러나 비입자성 스테로이드제제를 사용한 경우 스테로이드제제를 사용하지 않은 경우와 그 위험도에서 차이가 없었다. 따라서 신경학적 합병증의 발생을 예방하려면 경흉추 레벨의 경막외 주사를 시행하는 경우에 있어 입자성 스테로이드제제 사용을 피하는 것이 좋을 것이라는 과학적 근거를 확보한 것으로 판단된다.

주요어: 경막외 주사; 스테로이드; 신경학적 합병증; 성향점수; 코호트연구

학번: 2012-30571

감사의 글

대학원 예방의학 학위 과정을 시작한지가 어느새 10 년전이었습니다. 석사 과정 그리고 박사 과정을 무사히 마칠 수 있게 항상 많은 가르침을 주셨던 박병주 교수님께 우선 감사의 말씀을 드리고 싶습니다. 또한 바쁘신 와중에도 박사 심사를 맡아 주시고 더 나은 연구가 될 수 있도록 도와주셨던 윤병우 교수님, 정선근 교수님, 홍윤철 교수님 그리고 송홍지 교수님께도 감사드립니다.

학위 과정을 진행하는 동안, 재활의학과, 신경과 그리고 통증의학 분과 전문의 수련을 마치고, 이제 독립적인 전문가로서 새로운 시작을 박사 과정의 마무리와 같이 하게 되었습니다. 또한, 개인적으로는 결혼을 하고 가정을 이루어 한 아이의 아버지가 되었습니다, 앞으로 개인적으로는 행복한 가정을 이루고, 사회적으로는 전문가로서 사회에 기여하도록 노력하겠습니다.

마지막으로 사랑하는 아내 슬기와 귀여운 딸 지우 그리고 항상 저를 위해 기도해 주셨던 어머니에게 사랑과 감사의 말을 전합니다.

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